REMARKS

The Final Office Action of January 13, 2007 presents the examination of claims 1-3 and 5-8. These claims remain pending and are not further amended. Claims 9 and 10 are added.

Support for new claims

New claims 9 and 10 are identical in their recitations to previously presented claims 1 and 5, respectively, except that the amount of DNA used is recited as a ratio of 0.1 to 0.4 ng. DNA per site typed. Support for new claims 9 and 10 is provided by the working example 3 in the specification.

Written description

Claims 1-3 and 5-8 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description support in the specification. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

In particular, the Examiner asserts that the recitation in the claims that "at least 98% of single polynucleotide polymorphisms are detected" at a level of input genomic DNA of 10 to 40 ng represents "new matter" not previously described in the specification. Applicants disagree.

The Examiner asserts that the specification does not provide the specific language "at least 98% of single polynucleotide polymorphisms are detected". The Examiner further asserts that the language recited is not any rephrasing, correction of obvious error or description of any inherent function, theory or advantage of the invention. The Examiner does acknowledge that the specification provides an example in which the result stated ("at least 98% of single polynucleotide polymorphisms are detected") is achieved, but asserts that is insufficient because the specification only describes this result in experiments using 40 ng of DNA for amplification of 100 sites. That is, the Examiner seems to fail to find support for the bottom end of the range stated in the claims (10 ng of DNA per 100 sites).

Again, Applicants reiterate that the specification makes very clear that the method claimed is useful with as little as 0.1 ng per one site to be typed. The Examiner himself points out such disclosure presented in Example 3 .

The Examiner also urges that "claim[1] does not recite that 10-40 ng per 100 SNP sites is used in an INVADER assay or a TAQMAN PCR assay." (Emphasis in original.) Again, this is not understood. The INVADER assay or TAQMAN assay is expressly stated in claim 1 (and in new claim 9).

The Examiner asserts that this disclosure is insufficient because "the claims do not recite what Applicants are contending." This is not at all understood. 10-40 ng of DNA for use in typing each 100 polymorphic sites is plainly recited in claim 1. This is a ratio of 0.1 to 0.4 ng per site typed. In any event, new claims 9 and 10 are an attempt to recite the invention in language that more closely tracks the exact words of the specification. Though not legally required, this seems to be what the Examiner is requesting.

The Examiner asserts that, "The fact that the claims require that at least 98% of SNPs are detected necessarily require[s] that at least 98 SNP sites are successfully amplified using 10 ng of DNA in a simultaneously [sic] amplification. The specification does not have any support for this limitation, and thus the rejection is maintained." Applicants disagree, for all of the reasons mentioned previously, including those reiterated here:

> The present invention relates to improvements in multiplex assays for genotyping. The specification provides an example in which 98 of 100 SNP sites are successfully typed using 40 ng of input DNA. The specification also provides an example (Example 4) in which a single site is typed using only 0.1 ng of DNA template, and this example also explains that the multiplexed example (Example 3) may therefore be performed using as little as ¼ the amount (*i.e.* 10 ng per 100 SNP sites) used in Example 3. The specification also alleges that successful typing of, *e.g.* 100,000 sites can be obtained using approximately 10 μg of DNA template (see page 12, line 20).

[1] Which claim is not stated.

> The Examiner has not provided any evidence or reasoned statement as to why the results of Examples 3 and 4 are not general. Thus, his assertion that the recitation in the claims that 98% success rate in typing in a multiplex assay according to the invention is "new matter" is not persuasive.

As has been explained previously, the present invention relates at least in part to the finding that a high success rate of genome typing can be obtained using a ratio of the amount of DNA in the range of 0.1 to 0.4 ng per 100 sites to be typed, i.e. that the typing reaction is scalable with high success, provided that the recited range for this parameter is observed. This aspect of the invention is plainly shown in the working examples, at least examples 3 and 4, as explained previously. This aspect of the invention is reflected in the present claims in that they recite a ratio of template DNA consistent with the input ratio of 0.1 ng per SNP site (page 12, lines 21-22) or 10 to 40 ng per 100 SNP sites (Examples 3 and 4). (Claim 5 recites a limit the number of sites assayed to within this ratio.) Applicants submit that there is adequate written description of the invention as recited in the present claims 1-3 and 5-8, and accordingly the instant rejection should be withdrawn.

Obviousness

Claims 1, 3, 5 and 7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Mein et al. in view of Wang et al.. Claims 2, 6 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over these references and further in view of Brookes. These rejections are respectfully traversed. Reconsideration and withdrawal thereof are requested.

In particular, the Examiner fails to establish *prima facie* obviousness of the claimed invention. The combined teachings of the references do not disclose or suggest all of the features of the claims. At least the rate of typing of 98% of input loci is not described by the references. A success rate of 100% of typing[2] of 279 of 558 SNP sites as described by Wang is not "at least 98%" successful detection of the sites typed. It is only 50% successful detection of the sites typed. In fact, Wang discloses that amplification of 23 loci, 46 loci or 96 loci resulted

[2] Not "amplification".

in successful typing of only 92%, 90% or 85% of the loci, respectively. This is far from 100% success. The Examiner's supposition at the 3rd paragraph on page 10 is not correct. For the Examiner to assert otherwise suggests an inappropriate interpretation of the claims.

Furthermore, Applicants have previously explained that the rate of successful typing is not a linear function of the input DNA amount or the number of loci amplified at once. Rather, failures of the typing assays occur at least partly due to primer dimer formation and annealing of primers to secondary (*i.e.* not the target locus) sites in the genome. The Examiner provides no basis whatsoever for his assumption of a linear correlation between typing error rate and the number of loci typed with a given amount of DNA template.

The Examiner also attempts to deflect the deficiencies of the references by pointing out that "redesigning" of the assays is suggested as a remedy for their failure. However, no hint as to what should be done to redesign the assay is provided by the references, and therefore this disclosure is tatamount only to an invitation to experiment to improve the assay. Certainly there is no suggestion whatsoever that to adjust the amount of template DNA to the number of sites typed to fall in the range of 10-40 ng per 100 sites. Nor is there any suggestion to use the TAQMAN or INVADER assays for detection of the polymorphisms. Therefore the Examiner fails to establish *prima facie* obviousness of the present claims and the instant rejections under 35 U.S.C. § 103(a) over Mein, Wang and Brookes should be withdrawn.

In addition, Applicants submit that the finding that about 0.1 ng of template DNA could be used in combination with the Invader assay to obtain a successful SNP typing rate of $\geq$ 98% (*see*, Example 3 at pp. 18-19 of the specification) is an unexpected result that rebuts any assertion of *prima facie* obviousness. Applicants provide further evidence of unobviousness of the invention in the attached (unsigned) Declaration of Dr. Nakamura.[3]

[3] The Declaration as submitted has been returned to Dr. Nakamura for review and signature and a final, signed version of the Declaration will be submitted in a supplement to this paper.

Dr. Nakamura's Declaration provides data from an experiment in which 96 distinct SNP loci were typed using 20 different samples of genomic DNA, with an input amount of only 0.1 ng per locus typed, with a success rate of over 98% in all instances, and a success rate of 100% in 14 of 20 of the experiments. Therefore, the pending claims 1-3 and 5-10 should be found patentable over the references of record for this additional reason.

In view of the above amendment, arguments and experimental data, Applicants submit that the present application is in condition for allowance, and such favorable action is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell (Reg. No. 36,623) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

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Respectfully submitted,

By /mjn/

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Attachment: unsigned copy of Nakamura Declaration